example, page 10, line 14 to page 12, line 28 of the specification. No new matter has been added. Upon entry of the present amendment, claims 39-42, 44, 46-64, and 77-98 will be pending.

As a preliminary matter, Applicants acknowledge receipt of the "Attachment for PTO-948" outlining changes for prosecution of applications containing drawings. Formal drawings have been filed on date even herewith under separate cover to the Draftsperson.

Applicants acknowledge the Examiner's citation of U.S. Patent No. 5,877,399 at page 10 of the Office Action. Applicants note, however, that the reference was not used to reject the claims. Applicants will address this reference at such time as a rejection is based thereon.

I. Obviousness-Type Double Patenting

Claims 39-64 stand rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-10 of U.S. Patent No. 6,284,944. Although Applicants disagree, to advance prosecution of the present application, Applicants will file a Terminal Disclaimer upon an indication of allowable claims.

II. The Claimed Inventions Are Sufficiently Enabled

Claims 39-64 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to provide an enabling disclosure. Applicants traverse the rejection and respectfully request reconsideration because one skilled in the art would be able to practice the claimed invention without being required to perform undue experimentation.

As a preliminary matter, the Office Action proposes at page 5 that Applicants' invention is directed to "a gene-targeted mammal (knock-in mouse which is a transgenic mouse) ..." This is not correct. Applicants' claimed gene-targeted mammals were created using the gene-targeted approach, which is distinguished from the transgenic approach as set forth at page 4, line 18 to page 5, line 2 of the specification. Applicants' request that the Examiner keep this in mind when examining both the specification and the claims.

The Office Action appears to present only two reasons for alleging that Applicants' claimed inventions are not enabled. First, the claims are not enabled for non-rodent mammals. Second, the

specification allegedly does not provide sufficient description or guidance for producing mammals having particular phenotypic traits. Each of these reasons is addressed below in detail.

The Office Action asserts at pages 4-9 that the specification is not enabling for mammals other than rodents. Although Applicants disagree, to advance prosecution of the present application, claims 39-42, 44, 46-52 and 57-60 have been amended to recite "rodent." Claims 43 and 45, which recite "rodent" have been cancelled. In addition, Applicants thank the Examiner for indicating at page 4 of the Office Action that Applicants' specification is enabling for a gene-targeted rodent heterozygous for human PS-1 mutation comprising the human P264L mutation, and also comprising the Swedish mutation. The Examiner also asserts at page 8 of the Office Action that it is apparent that a skilled artisan can reasonably extrapolate from the exemplified mouse to a rodent having the same DNA constructs embedded in the genome. Thus, Applicants have added new claims 77-96 directed to this and related subject matter.

The reasoning directed to the alleged lack of evidence that the claimed mice exhibit a desired phenotype, such as displaying phenotypic expression of familial Alzheimer's disease, is misplaced. **Applicants' claims DO NOT require that the claimed rodents exhibit symptoms of FAD or any other phenotype.** In contrast, Applicants are only required to teach one skilled in the art to make and use the claimed invention -- a gene-targeted rodent that is homozygous or heterozygous for human PS-1 mutation. Applicants provide real working examples of preparation of a claimed rodent. Thus, there can be no question that Applicants teach one skilled in the art to make and use the claimed invention. The claimed rodents can be used in, for example, methods for screening compounds for the ability to decrease *in vivo* levels of Aβ42 peptide, as recited throughout the specification. One skilled in the art can clearly administer any compound to a claimed rodent treated with a compound and determine the amount of Aβ42 peptide in a tissue sample from the rodent. The Office Action does not provide any reasons why one skilled in the art would be required to perform undue experimentation to carry out the steps recited in any of the claimed methods. To advance prosecution of the present application, claims 39 and 40 have been amended to further recite that the Aβ42 protein level is elevated relative to the Aβ42 protein level in a wild-type mouse.

Thus, there is no reason to believe that one skilled in the art would be required to perform any amount of undue experimentation in order to make and use the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

III. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 564-8906 if there are any questions regarding Applicants' claimed invention. Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 1-38, 43, 45, and 65-76 have been cancelled.

New claims 77-98 have been added.

Claims 39-42, 44, 46-52 and 57-60 have been amended as follows:

39. (Amended) A gene-targeted, non-human [mammal] rodent heterozygous for a human Familial Alzheimer's Disease (FAD) mutation comprising a human mutation of the presenilin-1 (PS-1 gene), and a human transgenic for Swedish APP695, wherein the Aβ42 protein level is elevated relative to the Aβ42 protein level in a wild-type rodent.

40. (Amended) A gene-targeted, non-human [mammal] rodent homozygous for a human Familial Alzheimer's Disease (FAD) mutation comprising a human mutation of the presenilin-1 (PS-1 gene), and a human transgenic for Swedish APP695, wherein the Aβ42 protein level is elevated relative to the Aβ42 protein level in a wild-type rodent.

41. (Amended) The [mammal] rodent of claim 39 wherein said mutation of said PS-1 gene is P264L.

42. (Amended) The [mammal] rodent of claim 40 wherein said mutation of said PS-1 gene is P264L

44. (Amended) The [mammal] rodent of claim 43 wherein said [mammal] rodent is a mouse.

46. (Amended) The [mammal] rodent of claim 45 wherein said [mammal] rodent is a mouse.

47. (Amended) Generational offspring of the [mammal] rodent of claim 39 wherein said mutant PS-1 gene is expressed.

48. (Amended) Generational offspring of the [mammal] rodent of claim 40 wherein said mutant PS-1 gene is expressed.

49. (Amended) A method for screening chemical compounds for the ability to decrease *in vivo* levels of the Aβ peptide, said method comprising the steps of:

a) administering said chemical compound to the [mammal] rodent of claim 39; and

b) measuring the amount of Aβ peptide in a tissue sample from said [mammal] rodent, wherein a decrease in the amount of Aβ peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said Aβ peptide.

50. (Amended) A method for screening chemical compounds for the ability to decrease *in vivo* levels of the Aβ peptide, said method comprising the steps of:

a) administering said chemical compound to the [mammal] rodent of claim 40; and

b) measuring the amount of Aβ peptide in a tissue sample from said [mammal] rodent, wherein a decrease in the amount of Aβ peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said Aβ peptide.

51. (Amended) A method for screening chemical compounds for the ability to decrease *in vivo* levels of the Aβ peptide, said method comprising the steps of:

a) administering said chemical compound to the [mammal] rodent of claim 47; and

b) measuring the amount of Aβ peptide in a tissue sample from said [mammal] rodent, wherein a decrease in the amount of Aβ peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said Aβ peptide.

52. (Amended) A method for screening chemical compounds for the ability to decrease *in vivo* levels of the Aβ peptide, said method comprising the steps of:

a) administering said chemical compound to the [mammal] rodent of claim 48; and

b) measuring the amount of Aβ peptide in a tissue sample from said [mammal] rodent,

wherein a decrease in the amount of Aβ peptide in said tissue sample is indicative of a chemical compound that has the ability to decrease *in vivo* levels of said Aβ peptide.

57. (Amended) A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

a) administering a compound to the [mammal] rodent of claim 39; and

b) measuring the amount of Aβ peptide in a tissue sample from said [mammal] rodent, wherein a decrease in the amount of Aβ peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

58. (Amended) A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

a) administering a compound to the [mammal] rodent of claim 40; and

b) measuring the amount of Aβ peptide in a tissue sample from said [mammal] rodent, wherein a decrease in the amount of Aβ peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

59. (Amended) A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

a) administering a compound to the [mammal] rodent of claim 47; and

b) measuring the amount of Aβ peptide in a tissue sample from said [mammal] rodent, wherein a decrease in the amount of Aβ peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.

60. (Amended) A method for identifying a compound for treating Alzheimer's disease comprising the steps of:

a) administering a compound to the [mammal] rodent of claim 48; and

b) measuring the amount of Aβ peptide in a tissue sample from said [mammal] rodent,

wherein a decrease in the amount of Aβ peptide in said tissue sample is indicative of a compound that can be used to treat Alzheimer's disease.